UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

DATE: August 16, 1999

MEMORANDUM

SUBJECT: **MEVINPHOS**: **TOXICOLOGY CHAPTER FOR RED**

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Attached is the Toxicology Chapter for MEVINPHOS for the RED.

MEVINPHOS: TOXICOLOGY CHAPTER FOR RED

1. TOXICOLOGY DATA BASE

A. HAZARD CHARACTERIZATION

The Mevinphos data base is not complete, however there are sufficient data from the available studies for selecting acute and chronic dietary endpoints for an **import tolerance**.

Mevinphos is an organophosphate (OP) insecticide; its mode of toxic action is the inhibition of cholinesterase (ChE). In all studies in which ChE was measured, the Lowest Observed Adverse Effect Level (LOAEL) was based on either clinical signs of OP toxicity, plasma ChE inhibition or brain ChE inhibition (ChEI). In some studies, including both short-term and chronic administration, all three effects were seen at the LOAEL. Red Blood Cell (RBC) ChEI was not the basis for establishing any of the effect levels.

Mevinphos is a potent cholinesterase inhibitor at very low doses to rodents and rabbits. Female rats are more sensitive than males in many of the reviewed studies. The rat is more sensitive than the mouse; however this finding could be due to the method of oral administration. The chemical was administered by gavage in the rat studies but in the diet with the mouse carcinogenicity study. A bolus administration could have produced more toxicity than the gradual consumption of the chemical in the diet.

Mevinphos is acutely toxic to rats by the oral, dermal and inhalation routes (Toxicity Category I). Primary eye and skin irritation studies could not be conducted due to acute toxicity. Mevinphos is not a dermal sensitizer. There was no evidence of delayed neurotoxicity in the hen study. A confirmatory NTE study is required. Evidence of neurotoxicity was observed in most of the studies, however there was no evidence of alterations in structural neuropathological (gross and histopathology) measurements in an acute neurotoxicity study in rats. A subchronic neurotoxicity study is required due to findings in a human study in the literature in which neurological parameters were altered in men exposed to Mevinphos for 28 days.

There was no evidence of prenatal developmental toxicity or increased quantitative or qualitative fetal susceptibility in rats or rabbits. There was evidence of a qualitative increase in postnatal susceptibility in the range-finding study for the two-generation reproduction study. Due to the lethality in offspring treated by gavage on postnatal day (PND) 21 in the range-finding study, the timing of the direct treatment in the definitive two-generation reproduction study was delayed from PND 21 to PND 28. In the two-generation reproduction study, there was evidence of reproductive effects in both males and female in the F_1 generation. Offspring effects were seen at the same dose as the adult effects. A developmental neurotoxicity study (with extended postnatal treatment) is required based on the finding of qualitative increased susceptibility in the range-finding study.

There are no acceptable chronic toxicity studies in nonrodents. A waiver for the chronic toxicity study in dogs was granted due to emesis at low doses. In the mouse carcinogenicity study, there was no evidence of an increased incidence of neoplasms at doses which were adequate for testing the carcinogenic potential of the chemical. In the rat combined chronic toxicity/carcinogenicity study, evidence of chronic toxicity was limited

to clinical signs of toxicity and ChEI. Female rats had significant increasing trends in liver adenomas ($p<0.05$) and adenomas and/or carcinomas combined ($p<0.01$), however there were no statistically significant differences in the pair-wise comparisons of the dosed groups with controls. Therefore, it was determined that Mevinphos does not pose a cancer hazards to humans.

The mutagenicity data base is not complete. The available data do not unequivocally show that Mevinphos is genotoxic.

In the rat, Mevinphos is readily absorbed from the GI tract and is eliminated primarily as expired CO_2 or secondarily in the urine. The fraction of urinary excretion was increased with increasing doses. Four urinary metabolite fractions were isolated from female and male rats and the metabolite pattern was similar between sexes. None of the metabolites are of toxicological concern.

B. ACUTE TOXICITY

Table 1 summarizes the acute toxicity data for Mevinphos. The available studies satisfy the acute toxicity data requirements) for Mevinphos. The chemical is very acutely toxic by the oral, dermal and inhalation routes (Toxicity Category I). Primary eye and skin irritation studies were waived due to the severe toxicity. The dermal sensitization study in the guinea pig was negative.

Table 1: Acute Toxicity of Mevinphos

Guideline No.	**Study Type**	**MRID #(S).**	**Results**	**Toxicity Category**
81-1	Acute Oral - Rat	40570701	LD_{50} =3.5 mg/kg (M) 2.3 mg/kg (F) 2.8 mg/kg (M+F)	I
81-2	Acute Dermal - Rabbit	40570702	LD_{50} = 51 mg/kg (M) 60 mg/kg (F) 54 mg/kg (M+F)	I
81-3	Acute Inhalation - Rat	40600001	LC_{50} = 0.012 mg/L (M) 0.0073 mg/L (F) 0.0098 mg/L (M+F)	I
81-4	Primary Eye Irritation	Waived		
81-5	Primary Skin Irritation	Waived		
81-6	Dermal Sensitization - Guinea pig	40570703	non-sensitizer	

C. SUBCHRONIC TOXICITY

There was no acceptable subchronic toxicity study in nonrodents. In an acceptable subchronic oral toxicity study in rats, at the LOAEL, clinical signs of toxicity and decreased plasma ChE were observed in both sexes; brain ChEI was also observed in males. A summary of the study follows.

Subchronic Oral Toxicity in the Rat

In a subchronic toxicity study (MRID 42588501), 10 Crl:CDBR rats/sex/group were administered Mevinphos [89.89% a.i. (74.8% alpha isomer, 15.09% beta isomer)] by gavage for 90 days at doses of 0.05, 0.50, 1.0 or 1.5 mg/kg/day in males and 0.01, 0.05, 0.50 or 0.75 mg/kg/day. Due to mortality in the HDT males, the dose was reduced from 1.5 mg/kg/day to 1.0 mg/kg/day on Day 36.

Treatment-related deaths were seen in the 0.5 mg/kg/day (1 female), 1.0 (5 males) and 1.5 mg/kg/day (5 males) groups. Clinical signs of toxicity (pinpoint pupils in males and females, fine tremors in males) were observed consistently in the 1.0 and 1.5 mg/kg/day males and in the 0.5 and 0.75 mg/kg/day females beginning on Day 1. Additional clinical signs (coarse tremors, clear oral and/or ocular discharge, urine staining and soft stool, wet rales and hypoactivity) were observed with increasing incidence as the study progressed in these groups. Pinpoint pupils were observed consistently from Day 15 to the end of the study in the 0.5 mg/kg/day males and sporadically throughout the study in the 0.01 mg/kg/day females and 0.05 mg/kg/day males. These findings are of questionable toxicological significance in the latter two groups since the incidence was low and there were no alterations in plasma or brain cholinesterase.

There were no statistically significant changes in body weight. Overall body weight gain was reduced minimally in the 1.5 mg/kg/day males (8% decrease as compared to control) and 0.75 mg/kg/day females (12% decrease). There was a statistically significant increase in cholesterol in the 1.0 mg/kg/day males, however the magnitude of the increase (41.5 mg/dL vs 28.8 mg/dL in control) is minimal and of questionable toxicological significance.

For plasma cholinesterase (ChE), at the interim assay (Day 44/45), there was a decrease of 47-52% (as compared to the control value) in males dosed at 0.50 mg/kg/day and above and 22-73% in females dosed at 0.05 mg/kg/day and above. All were statistically significant, except for the 0.05 mg/kg/day females. At the terminal assay, plasma cholinesterase was reduced 46-57% in males dosed at 0.50 mg/kg/day and above and 23-79% in females dosed at 0.05 mg/kg/day and above. All were statistically significant, except for the 0.05 mg/kg/day females. For RBC ChE, at the interim assay, there were no statistically significant changes. At the terminal assay, there were statistically significant differences (9-12%) in males dosed at 0.05 mg/kg/day and above. These changes were not considered toxicologically significant due to the magnitude of the difference between treated and control values. There were no statistically significant differences in females. Brain ChE was decreased 41-56% in the 0.50 and 1.0 mg/kg/day males and 53-58% in the 0.50 and 0.75 mg/kg/day females. On histopathological examination at necropsy, there was a slight increase in the incidence of hepatocellular vacuolization in the 1.5 mg/kg/day males.

No Observed Adverse Effect Level (NOAEL) = 0.05 mg/kg/day in males and 0.01 mg/kg/day in females. Lowest Observed Adverse Effect Level (LOAEL) = 0.50 mg/kg/day in males and 0.05 mg/kg/day in females based on clinical signs of toxicity and decreased plasma cholinesterase in males and females and brain cholinesterase in

males.

This subchronic toxicity study is classified **Acceptable/Guideline** and does satisfy the guideline requirement for a subchronic oral study (OPPTS 870.1300; OPP 82-1) in rodents.

D. CHRONIC TOXICITY AND CARCINOGENICITY

There are no acceptable chronic toxicity studies in nonrodents. A waiver for the chronic toxicity study in dogs was granted due to emesis at low doses. In the mouse carcinogenicity study, there was no evidence of an increased incidence of neoplasms at doses which were adequate for testing the carcinogenic potential of the chemical. In an acceptable rat combined chronic toxicity/carcinogenicity study, evidence of chronic toxicity was limited to clinical signs of toxicity and ChEI. There was an increased incidence of hepatocellular adenomas in males and females and carcinomas in females of the high dose group; the incidence was within the laboratory's historical control range for adenomas in males but not for females. A statistical analysis of the study results was conducted by the Health Effects Division (HED). The analysis showed that female rats had significant increasing trends in liver adenomas ($p<0.05$) and adenomas and/or carcinomas combined ($p<0.01$). There were no significant differences in the pair-wise comparisons of the dosed groups with the controls. There was no statistically significant increase in tumors in male rats. It was determined that Mevinphos did not pose a cancer hazard to humans and a formal Cancer Assessment Review Committee meeting was not required (HED Doc. No. 013678). The bases for this determination were: 1) there was no pair-wise statistically significant increase in tumors; 2) there are equivocal findings in the mutagenicity studies, which do not support the increases in liver tumors; 3) the mid dose in the rat chronic toxicity/carcinogenicity study was adequate to test the carcinogenicity potential of Mevinphos (based on ChE inhibition) and no tumors occurred at this dose.

Carcinogenicity Study in the Mouse

In a mouse carcinogenicity study (MRIDs 41016201 and 41636801), 50 CD-1 mice/sex/group were treated with Mevinphos (66.5% alpha isomer and 21.2% beta isomer) in the diet for 18 months at doses of 0, 1.0, 10.0 or 25 ppm (males: 0.1, 1.5 and 3.7 mg/kg/day; females: 0.1, 1.9 and 4.8 mg/kg/day).There were no treatment-related effects, except for statistically significant decreases, although minimal ($\leq$ 7% decrease) in body weight at the beginning of the study. Body weight gain was also decreased for the first few weeks of the study. The NOAEL is 10.0 ppm (males: 1.5 mg/kg/day; females: 1.9 mg/kg/day); the LOAEL is 25.0 ppm (males: 3.7 mg/kg/day; females: 4.8 mg/kg/day) based on minimal body weight/body weight gain decreases at the beginning of the study.

There was no increased incidence of neoplasms in the treated groups. Although there were minimal effects in this study, there is evidence from the range-finding study that the doses were adequate to test the carcinogenic potential of the chemical. Dose selection was based on cholinesterase changes in a three month range-finding study using doses of 0, 0.5, 1.0, 2.0 or 10.0 ppm. At termination, plasma cholinesterase levels were decreased 26 and 62% in the 2.0 and 10.0 ppm group males and 46% in the 10 ppm group females. Brain cholinesterase was decreased 16 and 22%, respectively, in the 10 ppm group males and females. There were no other treatment-related changes in the study. Cholinesterase levels were not measured in the carcinogenicity study, however it can be assumed that plasma and brain cholinesterase would have been significantly affected at both the 10.0 and 25.0

ppm doses.

The study is classified **Acceptable (Guideline)** and **satisfies** the requirements for a mouse carcinogenicity study (OPPTS 870.4200; §83-2)

Combined Chronic Toxicity/Carcinogenicity Study in the Rat

In a combined chronic toxicity/carcinogenicity study (MRID 43088601), Mevinphos (85.74% a.i.) was administered orally by gavage 5 days/week to a total of 80 Sprague-Dawley rats/sex/group) at nominal dose levels of 0, 0.025, 0.35, or 0.70 mg/kg/day for approximately 104 weeks. The high-dose females received 0.70 mg/kg/day until day 82 of the study; on day 83 the dose was lowered to 0.60 mg/kg/day due to signs of acute toxicity. Ten (10) rats/sex/dose each were designated for cholinesterase determination, hematology, and clinical chemistry analyses, and an additional 10 rats/sex/dose were terminated at approximately 52 weeks. The animals that provided blood samples were terminated at approximately 104 weeks. The carcasses of rats specified for cholinesterase measurements were discarded without pathological examination.

There were no treatment-related effects noted in food consumption, mean body weights or body weight gains. Palpable masses were observed at a similar incidence in all groups, including the controls. Hematologic, clinical chemistry, urinalysis, and ophthalmological parameters, as well as organ weights, and gross pathology were also similar in the treated and control groups.

The general condition, behavior, and appearance of treated animals at ≥6 hours post-dosing was unaffected by treatment. On days 681, 688, and 695, observations were performed 30 minutes to 6 hours post-dosing. Tremors was the most frequent finding in both high-dose and mid-dose animals. Other signs of cholinesterase inhibition, such as exophthalmus, oral discharge, and/or anogenital staining were also observed in the treated groups, more frequently in the high-dose males. These findings all decreased after 6 hours post dosing.

The high-dose males had more early deaths than expected due to acute toxicity. There were no statistically significant differences in female survivorship. Survival rates at the terminal sacrifice (104 weeks) were, 21, 27, 28, 15% in controls, low-, mid, and high-dose groups males, respectively; and 21, 21, 24, 22% in the corresponding female groups. Survival rates at 96 weeks were 37-51% in all groups.

Cholinesterase activity was decreased in mid- and high-dose animals; the decreases in enzyme activity were generally greater in the females. At the interim sacrifice, plasma cholinesterase activity was decreased in the high-dose (↓57-71%; $p \leq 0.01$) and mid-dose animals (↓38-59% statistically significant [$p \leq 0.01$] in females only). Decreases ($p \leq 0.05$ or ≤ 0.01) in brain cholinesterase activity were observed in the high-dose (↓53-55%) and in the mid-dose animals (↓27-43%) Erythrocyte cholinesterase was decreased only 6-8% (p=not significant) in the mid- and high-dose groups at this interval.

At 24 months, there were no surviving control females, only 3-4 surviving male controls, and only 2-3 rats/ dose group of the 10 rats/sex/dose pre-selected for determination of cholinesterase activity. The 24 month brain cholinesterase data were therefore not used for enzyme activity comparisons. Plasma cholinesterase activity in the main study high-dose animals was decreased ($p \leq 0.05$ or 0.01) at the 3, 6, 12, and 18 month intervals (↓47-

71%). In the mid-dose males and females, plasma ChE was statistically significantly decreased 41-51% and 50-67%, respectively. Decreases ($p \leq 0.05$ or ≤ 0.01) in erythrocyte cholinesterase activity were noted in the high-dose males at 6 months (↓9%) and 18 months (↓12%) and in the high-dose females at 3 (↓17%), 6 (↓20%), and 18 months (↓16%). In the mid-dose males, RBC ChE was statistically significantly decreased 6-11% at the 3 and 6 month measurements and 8-15% (not statistically significant) at the 12 and 18 month measurements. The only statistically significant difference in RBC ChE in females was at the 18 month measurement (13%), although the decreases at the other time points were 9-17%. There were no treatment-related changes in ChE in the 0.025 mg/kg/day males or females, except for a statistically significant decrease in RBC ChE at the 18 month time period in the 0.025 mg/kg/day females. However this effect was not considered toxicologically significant due to the magnitude of the change, i.e. a 8% decrease. In general, the changes in RBC ChE were not considered toxicologically significant due to the magnitude of the differences between treated and control groups.

There were no treatment related non-neoplastic lesions detected in the animals at any interval. There were no neoplasms observed at the interim sacrifice. An increased incidence of hepatocellular adenomas was observed in the high-dose males (2.9% treated vs 0% controls). However, the incidence was within laboratory historical control ranges (0-5%). In high-dose females, an increased incidence of hepatocellular adenomas (4.5% treated vs 1.4% controls) as well as hepatocellular carcinomas (1.5% treated vs 0 controls) were observed. The incidence of hepatocellular adenomas in high-dose females (4.5%) was not within laboratory historical control ranges (0-2%), but was within the published historical ranges cited by the Sponsor (1.4-21.7%; Mc Martin, et al; 1992; Toxicologic Pathology, 20 #2, pages 212-225).

The chronic LOAEL is 0.35 mg/kg/day in males and females based on decreased plasma and brain cholinesterase activity. The chronic NOAEL is 0.025 mg/kg/day in males and females.

The submitted study is classified as **acceptable/guideline (§83-5)** and does satisfy the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats.

E. DEVELOPMENTAL/REPRODUCTIVE TOXICITY

There are acceptable prenatal developmental toxicity studies in the rat and rabbit and an acceptable multigeneration reproduction study in the rat. In both the rat and rabbit developmental studies, there was no evidence of developmental effects in the fetuses at a maternally toxic doses. There was evidence of increased qualitative postnatal susceptibility in the range-finding study for the two-generation reproduction study. At 0.5 mg/kg/day, there were clinical signs of toxicity and increased acute lethality when the offspring were treated by gavage from PND 21 to PND 28 (the first week post-weaning). For this study, the LOAEL/NOAEL were quantitatively the same for parents and offspring, however there was a qualitative difference in the effects with post-weaning preadolescent offspring demonstrating much more severe toxicity than adults. In addition, the LOAEL may have been lower in the offspring if ChE, which was the basis for the parental LOAEL, had been measured in the pups.

Due to the lethality in offspring treated directly from PND 21 to PND 28, the timing of the direct treatment in the definitive two-generation reproduction study was delayed from PND 21 to PND 28. In the two-generation

reproduction study, the LOAEL/NOAEL for parental toxicity are lower than the reproductive/offspring LOAEL/NOAEL indicating no quantitative increased susceptibility, however the results are biased because direct dosing of the offspring did not commence until PND 28. In addition, ChE measurements were not done on offspring. Summaries of the studies follow.

Prenatal Developmental Toxicity Study in Rabbits

In a developmental toxicity study with revisions (MRIDs 41823801 and 42422201), Mevinphos (89.57% a.i.) was administered by gavage at 0, 0.05, 0.5, or 1.5 mg/kg/day to artificially inseminated rabbits (20 females/dose) on days 7-19 of gestation. At the high-dose level, maternal toxicity was characterized by one treatment-related death and clinical observations including hypothermia, ataxia, hyperpnea, and clear oral discharge on gestation day 18 in a single dam. In addition, mean overall body weight gains when corrected for gravid uterine weight were reduced in the high-dose females (↓174%, days 0-29, $p \leq 0.05$). There were no treatment-related effects in food consumption, gross pathologic findings, or cesarean section parameters at any dose level. When compared to concurrent controls, maternal toxicity was characterized by reductions ($p \leq 0.01$) in plasma cholinesterase levels at the mid- (↓33%) and high- (↓47%) dose levels; erythrocyte cholinesterase levels were lower ($p \leq 0.05$ or 0.01) than controls at the low- (↓6%), mid- (↓13%), and high- (↓18%) doses. The observed inhibition of erythrocyte cholinesterase is not considered toxicologically significant due to the magnitude of the differences between control and treated groups.

The maternal LOAEL is 0.5 mg/kg/day, based on decreased plasma cholinesterase activity. The maternal NOAEL is 0.05 mg/kg/day.

There were no treatment-related effects on various parameters (pre- and post-implantation losses, number of fetuses per litter), fetal deaths, fetal weight, or developmental parameters.

The developmental LOAEL was not observed. The developmental NOAEL is 1.5 mg/kg/day, the highest dose tested.

This developmental toxicity study is classified **acceptable /guideline (§83-3[b]; OPPTS 870.3700)** and does satisfy the guideline requirement for a developmental toxicity study in the rabbit.

Prenatal Developmental Toxicity Study in the Rat

In a prenatal developmental study in rats (MRID 40201401), Mevinphos (66.5% cis-isomer; 21.2% trans-isomer) was administered by gavage to 24 mated Sprague-Dawley CD rats/group from days 6 through 15 of gestation at doses of 0, 0.20, 0.75, 1.0 or 1.25 mg/kg/day. The dose volume was 10 ml/kg/day. The standard developmental study parameters were measured; cholinesterase measurements were not included.

Seven (7) dams in the 1.25 mg/kg/day group died during treatment, therefore this dose group was eliminated. Clinical signs prior to death were typical of organophosphate toxicity. Dose-related clinical signs of toxicity in the 1.0 mg/kg/day group included tremors, lethargy, excessive salivation and lacrimation, chromodacryorrhea, anogenital staining and soft stools. Two females in the 0.75 mg/kg/day group had tremors on Day 15 of gestation.

There were no treatment-related effects on body weights, body weight gain, gravid uterine weights or food consumption. There were no statistically significant differences between treated and control animals in pregnancy rate, number of corpora lutea/dam, implantations/dam, number of abortions, male/female ratio, number of live litters, number of fetuses/dam, number of live fetuses/dam and fetal weight. There was no evidence of a treatment-related effect on external, visceral or skeletal malformations and variations.

Maternal NOAEL = 0.2 mg/kg/day; Maternal LOAEL = 0.75 mg/kg/day based on clinical signs of tremors

Developmental NOAEL is ≥ 1.0 mg/kg/day (Highest dose tested); Developmental LOAEL is > 1.0 mg/kg/day

This prenatal developmental study is classified **Acceptable/Guideline** and does satisfy the guideline requirements for a prenatal developmental study (OPPTS 870.3700; OPP 83-4) in rats.

Multigeneration Reproduction Study in the Rat

In a 2-generation reproduction toxicity study (MRID 42122201), Mevinphos (89.57% a.i.) as an aqueous formulation was administered continuously, except as noted below, by gavage to 35 Crl:CD BR Sprague-Dawley rats/sex/dose at dose levels of 0, 0.05, 0.1 or 0.5 mg/kg/day. Exposure to P animals began at 7 weeks of age and lasted for 10 weeks prior to mating. F_1 pups selected to produce the F_2 generation were exposed to the same dosage as their parents at post-natal day (PND) 28 and continuously throughout the rest of the study. Treatment was started a week later than specified by the guidelines because of the excessive mortality observed in the range-finding study in which treatment was started at weaning. After approximately 11 weeks of treatment, F_1 offspring were paired to produce the F_2 litters that were necropsied at weaning. Mating to produce a second F_2b generation was not performed.

Treatment-related clinical signs were observed in the high-dose P females following dosing. Signs observed included ataxia (1 occurrence), fine (8 occurrences) or coarse (17 occurrences) tremors, pinpoint pupils (11 occurrences), and oral discharge (8 occurrences). All other P and F_1 groups did not exhibit any treatment-related clinical signs. There were no significant differences in body weight or body weight gain for P generation adults. In the F_1 adults, body weight was decreased at several intervals during premating, mating and post-mating, although the changes were of relatively low magnitude (6-8% decrease as compared to control values) and therefore of questionable toxicological significance. The high dose P females had decreased body weight gains during Days 0-4 (108%) and Days 0-21 (27%) of lactation; the values were not statistically significant but were toxicologically significant. In the F_1 high-dose males, mean male mating and fertility indices were reduced ↓17% and 22%, respectively, although not significantly. These values were outside of the laboratory's historical control ranges.

Plasma cholinesterase activity was reduced ($p<0.01$) in mid-(↓21%) and high-dose P males (↓44%) and in mid-(↓25%,$p<0.05$) and high-dose P females (↓60%, $p<0.01$). Brain cholinesterase activity was reduced ($p<0.01$) in high-dose males (↓42%) and females (↓49%). Mid-dose female brain cholinesterase activity was also significantly reduced ($p<0.01$), but the difference was small (↓6%) and not of toxicological concern.

F_1 adults had greater reductions in plasma and brain cholinesterase activities than P adults. Plasma cholinesterase activity was reduced 22%, 20%, and 44% ($p<0.01$) in low-, mid-, and high-dose males, respectively. In females, plasma cholinesterase activity was reduced 18% (p=not sign.), 29% ($p<0.01$), and 60% ($p<0.01$) in low-, mid-, and high-dose animals, respectively. Brain cholinesterase activity was reduced in males 6% ($p<0.05$) and 49% ($p<0.01$) in mid- and high-dose males, respectively. Brain cholinesterase activity was reduced ($p<0.01$) and in mid- (8%) and high-dose (51%) females. The reductions in brain cholinesterase activity in the mid-dose animals and plasma cholinesterase activity in low-dose females were too small to be considered of toxicological concern.

There were no treatment-related findings on necropsy of the P adults. In the F_1 males, the high-dose testes+epididymides weight was significantly reduced (↓12%, $p<0.05$). The relative testes+epididymides/body weight ratio was not statistically different from concurrent controls.
Relative ovarian weights were decreased in the high-dose F_1 dams (↓17%, $p<0.05$). The F_1 males at 0.5 mg/kg/day had an increase in multifocal or diffuse unilateral testicular atrophy (3/24 vs 0/13 in controls). The F_1 females at 0.5 mg/kg/day had an increased incidence of animals with decreased number of corpora lutea in the ovaries (11/35 vs 3/35 in controls).

No treatment-related effects on survival indices were observed at any time in the F_1 and F_2 litters. No treatment-related clinical signs were noted in the F_1 or F_2 litters. There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

Body weights were significantly decreased in high-dose male and female F_1 pups from (PND) 4 through 21 (↓10 -16%, $p<0.01$).

The LOAEL for parental toxicity is 0.1 mg/kg/day in females and 0.05 mg/kg/day in males based on inhibition of plasma cholinesterase activity. The parental NOAEL is 0.05 mg/kg/day in females and < 0.05 mg/kg/day (lowest dose tested) in males.

The LOAEL for reproductive/offspring toxicity is 0.5 mg/kg/day based on decreased male mating and fertility indices, decreased absolute weight of testes + epididymides, decreased relative weight of the ovaries, histological changes in testes and ovaries and decreased pup body weight. The reproductive/offspring NOAEL is 0.1 mg/kg/day.

The reproductive study in the rat is determined to be **Acceptable (§83-4)** and <u>does</u> satisfy the guideline requirement for a multi-generational reproductive toxicity study in rats.

F. MUTAGENICITY

The acceptable genetic toxicology studies on Mevinphos indicate that the compound was weakly mutagenic at high concentrations in *Salmonella typhimurium* TA100, produced equivocal results in the Chinese hamster ovary (CHO) cell forward gene mutation assay and induced a reproducible, significant and dose-related positive response for clastogenicity in CHO cells. Nevertheless, the evidence for genotoxicity is not strong and the test results should be interpreted with caution for the following reasons: 1) the weak positive findings in the bacterial

gene mutation assay at excessively high doses; 2) the equivocal increase in the mutation frequency (MF) of CHO cells was not reproducible and occurred at a severely cytotoxic dose; furthermore, the increased MF was within the generally accepted background MF for this cell line; and 3) the significant and dose-related increases in structural chromosome aberrations were only observed at levels that severely reduced the mitotic index (MI) and had cytotoxic effects on the monolayer. It is of note, that the rate of false positives in the chromosome aberration assays increases substantially when doses that reduce the MI to >40-50% of control are analyzed. Although the *in vitro* unscheduled DNA synthesis assay in rat hepatocytes is currently unacceptable but it can be upgraded; the results were negative. Finally, since mutagenicity was neither enhanced (bacteria) nor abolished in the presence of S9 activation (mammalian cells) and there is no indication of a genotoxic effect in cultured rat hepatocytes, the mutagenicity data do not support the findings from the 2-year rat bioassay showing an increase in liver tumors in only one species and one sex. The acceptable studies do not satisfy either pre-1991 or new mutagenicity guideline requirements. It is recommended that Mevinphos be tested in an *in vivo* cytogenetic assay and that the sponsor provide the necessary data to upgrade the UDS assay. Summaries of the submitted mutagenicity studies are presented below:

Gene Mutations

1) *Salmonella typhimurium* mammalian microsome gene mutation assays: Mevinphos (89.6% pure: 74.48% alpha isomer; 15.09% beta isomer) was weakly positive with reproducible, slightly >2-fold or approaching 2-fold increases in histidine revertants of strain TA100 at high concentrations (3333-10,000 μg/plate both with or without S9 activation). The mutagenic response was generally comparable under nonactivated or S9-activated conditions. Thus, it was concluded that S9 activation was not required to uncover the mutagenic response. The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a bacterial gene mutation assay (MRID No. 41295001).

2) *In vitro* mammalian cell forward gene mutation assay in Chinese hamster ovary (CHO) cells: Mevinphos (89.6% pure: 74.48% alpha isomer; 15.09% beta isomer) was equivocal for the induction of gene mutations with a non-reproducible significant increase at the highest nonactivated dose tested (1.0 μg/mL with relative survival of 16%) but negative in the presence of S9 activation up to cytotoxic concentrations ($\geq$1.4 μg/mL). The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a mammalian cell gene mutation assay (MRID No. 41306301).

Chromosome Aberrations

3) *In vitro* mammalian cell cytogenetic assay in CHO cells: Mevinphos (89.6% pure: 74.48% alpha isomer; 15.09% beta isomer) is positive with reproducible, significant and dose-related increases in cells with structural chromosome aberrations but only in the absence of S9 activation and only at doses (0.15-0.42 μg/mL) that cause marked reductions in the mitotic index (MI); reductions in the MI ranged from 42% at 0.15 μg/mL to 61% at 0.42 μg/mL. The S9-activated test material was not clastogenic up to cytotoxic doses (>1 μg/mL). The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for *in vitro* cytogenetic assay (MRID No. 41378701).

Other Mutagenic Mechanisms

4) *In vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes: The test is negative up to a cytotoxic level (0.3 μg/mL). Compound insolubility was, however, seen at $\geq$0.6 μg/mL, which is not consistent with the other *in vitro* mammalian cell assays. The study is classified as Unacceptable and does not satisfy the requirements for FIFRA Test Guideline 84-2 for a UDS assay (MRID No. 41378702) but can be upgraded if issues regarding the insolubility of the test material are resolved.

F. Metabolism

Available metabolism data are adequate to satisfy the guideline requirements and have delineated the metabolic pathway in the rat. There are no metabolites of toxicological concern. A summary of the study follows.

Metabolism Study

In a rat metabolism study (MRID 41951801), [C3-^{14}C] Mevinphos (~96% a.i.) was administered to five Sprague-Dawley rats/sex/dose as either a single intravenous dose at 0.15 mg/kg, a single oral dose at 0.15 or 1.5 mg/kg, or a single oral dose at 0.15 mg/kg following a 15-day pretreatment with non-radio labeled Mevinphos at 0.15 mg/kg.

[^{14}C] Mevinphos was readily absorbed from the GI tract of male and female rats following a single oral dose at 0.15 or 1.5 mg/kg. Within 2 hours of oral or intravenous dosing, 34-65% of the dosed radioactivity was expired as $^{14}CO_2$ in all dose groups. Within 8 hours of dosing, urinary excretion accounted for 12-21% of the dosed radioactivity, and was the second major route of elimination. Within 24 hours, expired $^{14}CO_2$ accounted for 61-78% of the dosed radioactivity and urinary excretion accounted for 16-24%. Only trace amounts of radioactivity were recovered in the feces (0.5-1.4%) or as organic volatiles (0.04-0.16%) within 24 hours of dosing. Of the remaining radioactivity, a total of 5.4-7.5% of the dose was recovered in the blood, tissues, and organs.

Dose level had an apparent effect on the rate of absorption and the route of excretion. Within 2 hours of administering a single oral dose of [^{14}C]Mevinphos at 1.5 mg/kg, approximately 42 and 34% of the administered dose was recovered as $^{14}CO_2$ from males and females, respectively. This compares to 58-65% of the dose expired as CO_2 by animals in the single and repeated low dose groups for the same interval. Within 24 hours, radioactivity recovered in expired air as $^{14}CO_2$ and volatile metabolites accounted for 61-62% of the administered dose for high-dose rats, compared to 71-78% for low-dose rats. Urinary excretion was higher in animals from the high-dose group, accounting for 23-24% of the dose by 24 hours after dosing, compared to 14-19% for the low-dose groups. Fecal excretion was similar between the sexes and dose groups, accounting for 0.5-1.4% of the dose.

In general, the distribution of radioactivity in tissues was similar between dose groups. The highest concentrations of radioactivity detected in all groups were: skin (2-3%), bone (0.1-1%), and liver (0.7-1%). Percent of administered dose was approximately 0.1% in kidneys of both sexes and 0.3-0.4% in whole blood.

Four urinary metabolite fractions were isolated from female and male rats and in general, the metabolite pattern was similar between sexes within each dose group. Pretreatment with Mevinphos, dose level, and the route of administration had no effect on the metabolite profile. For both sexes, metabolites identified in urine included cis-Mevinphos (0.6-3.0%), desmethyl cis-Mevinphos (2.0-7.0%), and cis-Mevinphos acid (2.3-9.3%). An unknown

multi-component polar fraction was also isolated from urine that accounted for 3.4-6.2% of the dose. Trans-Mevinphos was not detected in any urine sample.

This study is classified **acceptable** and satisfies the requirements for a metabolism study (**§85-1**).

G. Neurotoxicity

Neurotoxicity studies are limited to the acute delayed neurotoxicity study in the hen and acute neurotoxicity study in the rat. The hen study showed no evidence of delayed neuropathy, however neurotoxic esterase measurements were not conducted. In the rat study, clinical signs of toxicity, Functional Observational Battery changes and plasma and brain ChEI were all observed at the LOAEL.

Acute Delayed Neurotoxicity Study in the Hen

Three of ten hens dosed with 12.5 mg/kg of Mevinphos and antidotal doses of atropine and 2-PAM chloride died. The seven surviving hens were dosed a second time on day 21 at 12.5 mg/kg. Clinical signs observed during the first week included ataxia, hypoactivity, prostration, sitting on hocks, wings outstretched, hypopnea, closed eyes, miosis, leg weakness, and soft stools. Food consumption was decreased, but body weight gain was not affected. There was no evidence of delayed neurotoxicity. No histopathologic lesions of nervous tissue could be found in any hens dosed with Mevinphos.

The positive controls were unaffected by tritolyl-phosphate administration on day 0, but classic delayed neurotoxicity was seen following administration with tri-o-cresyl phosphate on day 21. They had axonal swelling in the spinal cord, and axonal fragmentation and a loss of myelin sheath in the peroneal, tibial and sciatic nerve.

The study is classified as Core Minimum.

Acute Neurotoxicity Study in the Rat

In an acute neurotoxicity screening battery study (MRID 42985402), male and female rats (27 animals/sex/group; 17 animals/sex/group at the low dose) were given a single dose of Mevinphos (86.55% a.i.) in deionized water by gavage at levels of 0, 0.025, 0.1, 2.0, or 3.5 mg/kg. FOB, motor activity and cholinesterase activity were evaluated at 45 minutes, 7 and 14 days after dosing.

No significant differences were observed in body weight or body weight gains. Mean red blood cell cholinesterase values were comparable between all groups. No treatment-related changes in absolute or relative brain or brain region weights or brain dimensions were apparent in any of the test groups. No treatment-related histopathological lesions were observed in any of the treated groups. No alterations of toxicological significance occurred at days 7 and 14. The 0.025 and 0.1 mg/kg dose groups did not demonstrate any functional toxicity at day 0. Toxicological manifestations were limited to day 0 (peak effect approximately 45 minutes post-dosing) in the 2.0 and 3.5 mg/kg dose groups.

In the 2.0 mg/kg male and female rats, clinical signs were manifested as follows: gait alterations, whole body tremors, forelimb tremors, hindlimb tremors, repetitive jaw movement, salivation (males), right and left eye

exophthalmus (females), right and left eye lacrimation (females). During home cage observations, the following changes were considered treatment-related: altered posture (sitting, head held low) in both sexes, whole body tremors in both sexes, slight tremors in males and moderately coarse tremors in both sexes. During handling observations, increases in lacrimation and exophthalmus in both sexes were observed. During open field observations, the following were considered treatment-related: slightly or moderately impaired mobility in both sexes, altered gait (ataxia) in both sexes, whole body tremors in both sexes, repetitive jaw movements in males and tremors in both sexes. During sensory observations, the number of males and females with no pupil response was significantly different from controls. Lack of touch response in males, lack of startle response in both sexes, and lack of tail pinch response in males were also considered treatment-related. During neuromuscular observations, reduction of hindlimb resistance was increased for both sexes. During locomotor activity assessment, decreases in mean total ambulatory and locomotor activity counts in males and females were considered treatment-related. Mean plasma cholinesterase values were reduced in males (↓36%, $p<0.01$) and females (↓39%, $p<0.05$). In the brain, cholinesterase levels were reduced in males and females in the brainstem (↓20%, $p<0.05$; ↓25%, $p<0.01$, respectively).

In the 3.5 mg/kg group, one male and 5 females died on Day 0 following dose administration. Clinical signs of intoxication were manifested by 9/10 males and 10/10 females. Clinical observations consisted of gait alterations (rocking, lurching or swaying, or prostration), tremors (whole body, forelimb/hindlimb, and/or repetitive jaw movement), salivation, exophthalmus, lacrimation, clear material on the forelimbs, and rales (females only). During the home cage observations, the following were considered treatment-related in both sexes: altered posture (flattened posture and sitting, head held low), whole body tremors, repetitive jaw movements, tremors, and eyelids wide open. During handling observations, the following were treatment-related in both sexes: exopthalamus, increased lacrimation and increased salivation. An increase in gasping was observed in females, a decrease respiratory rate in males and increased red deposits around nose and mouth in males. During open field observations of the 3.5 mg/kg groups, the following parameters were considered treatment-related in both sexes: altered mobility (slightly and moderately impaired in both sexes, totally impaired in females), decreased normal gait and increased ataxia, increased clonic convulsions (whole body tremors, clonic tremors of the limbs and repetitive jaw movements), increased tonic convulsions, increased tremors (slight and moderately coarse in both sexes, extremely coarse in females), and decreased number of rearings. Females had an increase in time to first step and an increase in the number of head flicks. For sensory observations, the following were considered treatment-related in both sexes: diminished approach response, decreased touch response, increased number of animals with no pupil response and altered air righting reflex (slightly uncoordinated or lands on back). Females had a decreased tail pinch response and an increase in number with no eyeblink response. Neuromuscular parameters affected in both sexes included: increases in number with altered hindlimb extensor strength (reduced resistance) and decreased rotarod performance. Females had decreased forelimb grip strength. Physiological parameters affected in both sexes included increased catalepsy and decreased body temperature. Changes in locomotor observations in both sexes included decreased total ambulatory activity and total activity counts. Mean plasma cholinesterase values were reduced in high-dose males (41%) and females (47%). In the brain, cholinesterase levels were reduced in high-dose males in the brainstem (↓33%, $p<0.01$) and cortex (↓19%, $p<0.05$); in the high-dose females, reduced cholinesterase levels were noted in the hippocampus (↓36%, $p<0.05$), olfactory region (↓28%, $p<0.05$) and brainstem (↓31%, $p<0.01$).

The acute neurotoxicity LOAEL is 2.0 mg/kg based on an increased incidence of clinical signs, changes in the

majority of the FOB parameters and decreased plasma and brain cholinesterase. The acute neurotoxicity NOAEL is 0.1 mg/kg.

The submitted study is classified as **acceptable/guideline** (**§81-8**) and satisfies the guideline requirements for an acute neurotoxicity screening battery in rats.

II. FQPA Safety Factor Considerations

The following evaluation of the chemical Mevinphos is provided to address FQPA considerations on the sensitivity of infants and children.

There was no evidence of increased susceptibility in developing fetuses in the rat and rabbit prenatal developmental studies. There was evidence of increased qualitative postnatal susceptibility in the range-finding study for the two-generation reproduction study. At 0.5 mg/kg/day, there were clinical signs of toxicity and increased acute lethality (19.4% vs 2.8% in control group) when the offspring were treated by gavage from PND 21 to PND 28 (the first week post-weaning). For this study, the P generation LOAEL was set at 0.5 mg/kg/day based on ChE inhibition and reproductive effects; the NOAEL was 0.1 mg/kg/day. The F_1 generation LOAEL was set at 0.5 mg/kg/day based on effects on offspring mortality, growth and clinical signs of toxicity; the NOAEL was 0.1 mg/kg/day. Although the LOAEL/NOAEL were quantitatively the same for parents and offspring, there was a qualitative difference in the effects with post-weaning preadolescent offspring demonstrating much more severe toxicity than adults. In addition, the LOAEL may have been lower in the offspring if ChE, which was the basis for the parental LOAEL, had been measured in the pups.

Due to the lethality in offspring treated directly from PND 21 to PND 28, the timing of the direct treatment in the definitive two-generation reproduction study was delayed from PND 21 to PND 28. In the two-generation reproduction study (MRID 42122201), the LOAEL for reproductive/offspring toxicity was 0.5 mg/kg/day based on effects on the F_1 generation, including decreased pup weights during lactation, decreased male mating and fertility indices, decreased absolute weight of the testes + epididymides, decreased relative weight of the ovaries and histological changes in the testes and ovaries. The NOAEL for reproductive/offspring toxicity was 0.1 mg/kg/day. The LOAEL for parental toxicity was 0.1 mg/kg/day in females and 0.05 mg/kg/day in males based on decreased plasma cholinesterase activity. The NOAEL for parental toxicity was 0.05 mg/kg/day in females and <0.05 mg/kg/day in males. Although the LOAEL/NOAEL for parental toxicity are lower than the reproductive/offspring LOAEL/NOAEL indicating no quantitative increased susceptibility, the results are biased because direct dosing of the offspring did not commence until PND 28. In addition, ChE measurements were not done on offspring.

III. Toxicity End-Point Selection

On April 13, 1999, the HED Hazard Identification Assessment Review Committee (HIARC) evaluated the entire toxicological database for Mevinphos and selected the relevant toxicity endpoints, taking into consideration the use patterns and exposure information on this chemical. The selected toxicological endpoints and the doses for risk assessment are summarized in Table 2, and additional relevant details for each endpoint are presented. A copy of the HIARC Report, dated April 13, 1999, Document No. 013334] is appended.

Table 2: Mevinphos Toxicity Endpoints

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOEL= 0.1 mg/kg/day UF = 100	increased incidence of clinical signs, changes in the majority of the FOB parameters and decreased plasma and brain cholinesterase in males and females	Acute Neurotoxicity Study in Rats (MRID 42985401)
	Acute RfD = 0.001 mg/kg (General Population) **Acute RfD** for Females 13+ not proposed		
Chronic Dietary	NOEL = 0.025 mg/kg/day UF = 100	decreased plasma and brain cholinesterase activity in males and females	Combined Chronic Toxicity/Carcinogenicity Study in Rats (MRID 43088601)
		Chronic RfD = 0.00025 mg/kg/day	
Short-Term (Dermal)	NOEL=	Not required - import tolerance only	
Intermediate-Term (Dermal)	NOEL=	"	
Long-Term (Dermal)	NOEL=	"	
Short Term (Inhalation)	NOEL=	Not required - import tolerance only	
Intermediate Term (Inhalation)	NOEL=	"	
Long Term (Inhalation)	NOEL=	"	

III. **DATA GAPS**

The HIARC determined that the following studies are required:

1) *In vivo* cytogenetic assay and the necessary data to upgrade the UDS assay (MRID 41378702)

2) Confirmatory NTE Study in the Hen

There is an acceptable acute delayed neurotoxicity study in the hen which concluded that there was no evidence of Mevinphos-induced delayed neuropathy. However, NTE measurements were not conducted. It has been HIARC policy to request confirmatory NTE studies on all organophosphates when these measurements were not included in the original hen study.

3) Subchronic Neurotoxicity Study in the Rat

The HIARC acknowledged that there was no evidence of structural neuropathology in the acute neurotoxicity study after a single dose of Mevinphos. However, the Committee was concerned about alterations in neurological assessments in humans reported in a literature article. In a 1977 study by Verberk and Salle (summarized under Additional information from the literature), there was a 7% decrease in slow motor fiber nerve velocity and a 38% increase in Achilles tendon reflex force in males treated with Mevinphos at a dose of 25 μg/kg for 28 days. Therefore, a study in rats measuring in life and postmortem neuropathology parameters is required to assess if this finding is associated with subchronic treatment in animals.

3) Developmental Neurotoxicity Study in Rats

The HIARC expressed concern about possible long-term effects of postnatal exposure to Mevinphos. There were no studies which measured direct postnatal exposure for longer than 1 week. In the range-finding study, direct dosing by gavage was only administered from PND 21 to 28. In the two-generation reproduction study, offspring were possibly exposed to Mevinphos in the milk during lactation, but there was a no exposure from PND 21 to PND 28, at which time direct dosing commenced. In the protocol for a guideline Developmental Neurotoxicity Study, the test material is administered from Day 6 of gestation to Day 10 postnatally. The HIARC recommended that a developmental neurotoxicity study be conducted and that it be designed to extend the postnatal treatment period for offspring and to evaluate cholinesterase inhibition in the offspring. The registrant should contact Health Effects Division scientists to collaborate on study design.

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